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Attestation

EPO-DG 1

06.04.2001

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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99113502.1

PRIORITY DOCUMENT

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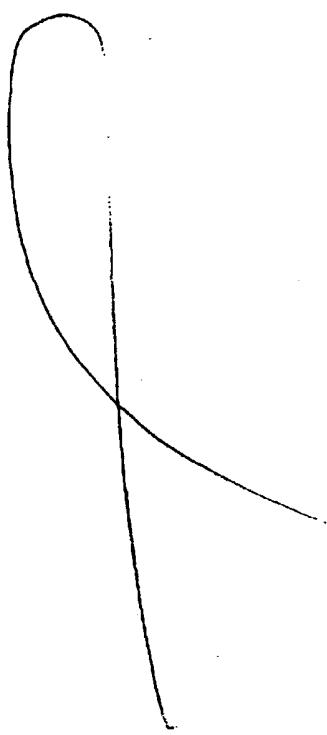
Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 29/05/00
LA HAYE, LE





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**Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation**

Anmeldung Nr
Application no
Demande n°
99113502.1

Anmeldetag
Date of filing
Date de dépôt
02/07/99

Anmelder
Applicant(s)
Demandeur(s)
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51368 Leverkusen
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Bezeichnung der Erfindung
Title of the invention
Titre de l'invention
Angiotropetin-7 and uses thereof

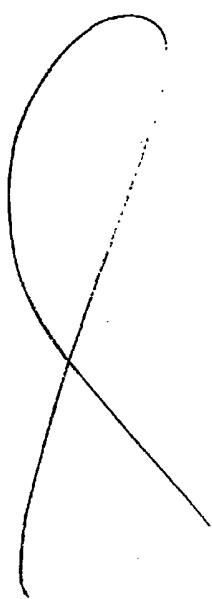
In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat State Pays	Tag Date Date	Aktenzeichen File no Numéro de dépôt
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Internationale Patentklassifikation
International Patent classification:
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Am Anmeldetag benannte Vertragstaaten
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt

Bemerkungen
Remarks
Remarques



- 1 -

EPO-Munich
53

02 Juli 1999

Angiopoietin-7 and uses thereof

The present invention provides a nucleic acid molecule encoding human Angiopoietin-7 (Ang-7) protein. In addition the invention provides methods for producing recombinant human Ang-7 protein. The invention also provides an antibody which specifically binds human Ang-7 protein. The invention further provides for therapeutic compositions as well as a method for modulating angiogenesis.

Introduction

10

The cellular behavior responsible for the development, maintenance, and repair of differentiated cells and tissues is regulated, in large part, by intercellular signals conveyed via growth factors and similar ligands and their receptors. The receptors are located on the cell surface of responding cells and they bind peptides of polypeptides known as growth factors as well as other hormone-like ligands.

20

The phosphorylation of tyrosines on proteins by tyrosine kinases is one of the key modes by which signals are transduced across the plasma membrane. Several currently known protein tyrosine kinase genes encode transmembrane receptors for polypeptide growth factors and hormones.

25

Growth factor receptors of endothelial cells are of particular interest due to the possible involvement of growth factors in several important physiological and pathological processes, such as vasculogenesis, angiogenesis, atherosclerosis, and inflammatory diseases. Also, the receptors of several hematopoietic growth factors are tyrosine kinases.

30

Receptor tyrosine kinases differ in their specificity and affinity. In general, receptor tyrosine kinases are glycoproteins, which consist of (1) an extracellular domain capable of binding the specific growth factor(s); (2) a transmembrane domain which usually is an alpha-helical portion of the protein; (3) a juxtamembrane domain where

the receptor may be regulated by, e.g., protein phosphorylation; (4) a tyrosine kinase domain which is the enzymatic component of the receptor; and (5) a carboxyterminal tail which in many receptors is involved in recognition and binding of the substrates for the tyrosine kinase.

5

A gene encoding an endothelial cell transmembrane tyrosine kinase, was described by Partanen, et al., Proc. Natl. Acad. Sci. USA, 87: 8913-8917 (1990). This gene and its encoded protein are called "Tie" which is an abbreviation for "tyrosine kinase with Ig and EGF homology domains." Partanen, et al. Mol. Cell. Biol. 12: 1698-1707 (1992).

10

Enhanced Tie expression was shown during neovascularization associated with developing ovarian follicles and granulation tissue in skin wounds. Korhonen, et al. Blood 80: 2548-2555 (1992). Thus, Tie has been suggested to play a role in angiogenesis, which is important for developing treatments for solid tumors and several other angiogenesis-dependent diseases such as diabetic retinopathy, psoriasis, atherosclerosis and arthritis.

15

Two structurally related TIE receptor proteins have been reported to be encoded by distinct genes with related profiles of expression. Both genes were found to be widely expressed in endothelial cells of embryonic and postnatal tissues. Significant levels of Tie-2 transcripts were also present in other embryonic cell populations, including lens epithelium, heart epicardium and regions of mesenchyme. Maisonpierre, et al., Oncogene 8: 1631-1637 (1993).

20

The predominant expression of the TIE receptor in vascular endothelia suggests that TIE plays a role in the development and maintenance of the vascular system.

25

Two ligands, angiopoietin-1 (Ang-1) and-2 (Ang-2), have been identified for Tie-2. Angiopoietin-2 is antagonistic to angiopoietin-1, preventing binding of the activating ligand and blocking its ability to stimulate Tie-2 kinase activity and autophos-

- 3 -

phorylation. Angiopoietin-1 and -2 do not bind Tie-1. Angiopoietin-1 and -2 are about 60% identical. They share a similar domain structure with a N-terminal coiled-coil region and a C-terminal fibrinogen-like domain.

5 Northern analysis shows that angiopoietin-1 is quite widely expressed, but that the expression of angiopoietin-2 is very limited. It is present only in tissues such as ovary, uterus, and placenta, which undergo vascular remodeling.

Recently, two additional ligands for the Tie-2 receptor were identified (Valenzuela et 10 al., Proc. Natl. Acad. Sci. 96: 1904-1909 (1999), Tie ligand-3 (angiopoietin-3 [Ang-3]) and Tie ligand-4 (angiopoietin-4[Ang-4]), but the precise physiological role of Ang 3 and 4 has not been reported yet. However, discovery of new members of the angiopoietin ligand family indicates that other members could exist.

15 Angiogenesis, concurrent with tissue development and regeneration, depends on the tightly controlled processes of endothelial cell proliferation, migration, differentiation and survival. Dysfunction of the endothelium is a key feature of many diseases including cancer, atherosclerosis, and diabetic angiopathies, to name but a few. Identification of novel Tie receptors and angiopoietins will shed light on the 20 details of how blood vessels are generated, remodelled, and eliminated, thus, providing new tools to improve therapeutic standards to above mentioned indications.

The invention is directed to the Ang-7 protein sequence, corresponding nucleic acid 25 sequences, antibodies, pharmaceuticals compositions, vectors and vector host systems according to the claims.

Ang-7 protein as well as the Ang-7 antibodies can be used in the treatment of diseases as defined above.

Description of the figures.

Fig. 1: Nucleotide sequence encoding human Ang-7.

Fig. 2: Deduced amino-acid sequence of human Ang-7. The sequence is shown in the one letter code of amino-acids.

5 Fig. 3: Alignment of the amino acid sequences of Ang-1, Ang-2, Ang -3, Ang-4 and Ang-7. Identical amino acids are highlighted by boxes.

Fig. 4: Expression profile of Ang-7.

Fig. 5: In vitro translation of Ang-7. Lane 1: Rainbow [¹⁴C]methylated protein molecular weight marker (Amersham, Little Chalfont Buckinghamshire, England) containing following proteins: ovalbumin (46 kDa), carbonic anhydrase (30 kDa), trypsin inhibitor (21,5 kDa), lysozyme (14,3 kDa), aprotinin (6,5 kDa). Lane 2: In vitro translation of Ang-7 using the T7 promoter of the mammalian expression vector pcDNA3.1/Myc-His(-) (Invitrogen, Groningen, Netherlands). Lane 3: In vitro translation of Ang-7 using the SP6 promoter of the mammalian expression vector pcDNA3.1/Myc-His(-) (negative control). Lane 4: Positive control from the in vitro translation system (Promega, Madison, USA).

Examples.**Example 1.**

5

With the goal to identify new members of the angiopoietin ligand family a BLAST search (Altschul et al., 1997) of the Expressed Sequence Tag (EST) database from the National Center for Biotechnology Information (NCBI) has been performed. The amino acid sequence of Ang-1 was used as a probe. As a result, a human EST with the accession Number AA773234 was identified. The identified EST showed significant homology to Ang-1 in the reading frame +2. The P value (probability) was $4,4 \times 10^{-28}$ which strongly indicates that the identified EST encodes a fragment of a novel protein which could belong to the family of angiopoietins. Further proof that the newly identified EST encodes a fragment of a novel angiopoietin (lateron designated as Ang-7) was obtained when a BLAST search of a Swissprot database was performed using the identified EST as a probe. The P values obtained for Ang-1 and Ang-2 were $3,2 \times 10^{-32}$ and $2,6 \times 10^{-34}$, respectively.

10

Because the commercial EST-clone providers were not able to deliver us the identified EST AA773234, we identified an other homologues EST which belongs to the same gene cluster. The corresponding EST-clone with the accession number AA255590 was purchased and analyzed. Sequencing analysis revealed that the clone AA255590 indeed encodes the fragment of the same gene and includes the sequence of EST AI773234.

15

Example 2.

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For the purpose of full length cloning of the Ang-7 cDNA the HUCL primary membranes (Stratagene, La Jolla, USA) were hybridized with the antisense probe, prepared as described in the example 4. Hybridization revealed a signal at the position L04. The corresponding secondary array membrane was purchased and

hybridized under the same conditions. The signal was detected at the position G19. Thus, the individual clone L04G19 was purchased and analyzed. The clone contained an insert of 2,2 kb. Sequencing analysis confirmed, that this cDNA clone contains the full length coding sequence of Ang-7.

5

Example 3.

Complete sequencing of the 2173 bp long L04G19 cDNA, which encodes Ang-7 (Seq ID 1, Fig. 1) revealed an open reading frame of 1432 bp which encodes a polypeptide of 493 amino acid residues (Seq. ID 2, Fig. 2). Alignment of the deduced amino acid sequence of Ang-7 with angiopoietins-1, -2, -3 and -4 is shown in Fig. 3. The N-terminal and C-terminal parts of the Ang-7 protein contain characteristic coiled-coil and fibrinogen – like domains, found also in other angiopoietins. The similarity index between the novel Ang-7 and Ang-1 and -2 is 23,9% and 23,5 %, 10 15 respectively.

20

Example 4.

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To study the expression profile of the identified novel Ang-7, the plasmid AA255590 was linearized with EcoRI and the antisense [³²P] radioactively labelled RNA probe was generated using Strip-EZ T3 kit (Ambion, Austin, USA) in accordance to the instructions of the manufacturer. An RNA master blot (Clontech Laboratories, Inc., Palo Alto, CA, USA) was hybridized with the generated probe. The hybridization and washing was performed as recommended in the manual of the Strip-EZ kit. After washing, the membrane was exposed to a phosphorimager screen, scanned on a Fuji Bas-1500 scanner, and the intensity of the radioactive signals was evaluated with the TINA 2.0 software (Raytest, Straubenhardt, Germany). The resulting histogram is

presented on Fig. 4. The novel *ang-7* gene is strongly expressed in heart tissues (atrium left and right, ventricle left and right), uterus, mammary gland and corpus callusum.

5 Expression of Ang-7 in many tissues encompassing a high circulation of blood, indicates that Ang-7, as Ang-1 and -2, could play a role in angiogenesis.

Example 5.

10 To test whether the *ang-7* cDNA can be translated to Ang-7 protein and to determine the molecular weight of Ang-7, the complete cDNA was amplified by PCR and cloned upstream of the T7 promoter in the Eco RV and Kpn I restriction sites of the mammalian expression vector pcDNA3.1/Myc-His(-) (Invitrogen, Groningen, Netherlands). For PCR amplification, a 5' primer

15 (5' GCGAATTCACCATGAGGCCACTGTGCGT 3') homologous to the 5' end of the *ang-7* cDNA was used in combination with a 3' primer (5' GGAAGCTTATGGAAGGTGTTGGGGTCGG 3') homologous to the 3' end of the Ang-7 cDNA. To increase translational efficiency a Kozak consensus sequence was integrated in the 5' primer. For cloning, recognition sequences for the restriction enzymes Eco RV and Kpn I were introduced into the 5' and 3' primers, respectively.

20 The in vitro translation was done essentially according to the instruction of the manufacturer (Promega, Madison, USA) using [³⁵S]methionine. The resulting reaction products were subjected to electrophoresis on a sodium dodecyl sulfate-12% polyacrylamide gel and visualized by autoradiography.

25 A major band of ~ 60 kDa was detected (Fig. 5). The observed molecular mass of the major band was slightly larger than the calculated molecular mass of recombinant Ang-7 (~57,1 kDa). However, since the amino acid sequence of Ang-7 contains several potential glycosylation sites the observed larger size of Ang-7 may be produced by incomplete glycosylation of the protein in the in vitro translation system.

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□ Gln Thr Ser Glu Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu

□ 180 185 190

□ Lys Lys Val Leu Ala Met Glu Asp Lys His Ile Ile Gln Leu Gln Ser

□ 195 200 205

- 18 -

Ile Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn
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 Ser Ile Ile Glu Glu Leu Glu Lys Lys Ile Val Thr Ala Thr Val Asn
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 Asn Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn
 245 250 255
 Asn Leu Leu Thr Met Met Ser Thr Ser Asn Ser Ala Lys Asp Pro Thr
 260 265 270
 Val Ala Lys Glu Glu Gln Ile Ser Phe Arg Asp Cys Ala Glu Val Phe
 275 280 285
 Lys Ser Gly His Thr Thr Asn Gly Ile Tyr Thr Leu Thr Phe Pro Asn
 290 295 300
 Ser Thr Glu Glu Ile Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly
 305 310 315 320
 Gly Trp Thr Ile Ile Gln Arg Arg Glu Asp Gly Ser Val Asp Phe Gln
 325 330 335
 Arg Thr Trp Lys Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly Glu
 340 345 350
 Tyr Trp Leu Gly Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln Arg
 355 360 365

- 19 -

□
Tyr Val Leu Lys Ile His Leu Lys Asp Trp Glu Gly Asn Glu Ala Tyr

□ 370 375 380
□

□
Ser Leu Tyr Glu His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr Arg

□ 385 390 395 400
□

□
Ile His Leu Lys Gly Leu Thr Gly Thr Ala Gly Lys Ile Ser Ser Ile

□ 405 410 415
□

□
Ser Gln Pro Gly Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp Lys

□ 420 425 430
□

□
Cys Ile Cys Lys Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe Asp

□ 435 440 445
□

□
Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg Gln

□ 450 455 460
□

□
Asn Thr Asn Lys Phe Asn Gly Ile Lys Trp Tyr Tyr Trp Lys Gly Ser

□ 465 470 475 480
□

□
Gly Tyr Ser Leu Lys Ala Thr Thr Met Met Ile Arg Pro Ala Asp Phe

□ 485 490 495
□

□

□

□

□

- 20 -

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□
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□

□
Thr Met Ala Ala Ala Gln His Arg Gly Pro Glu Ala Gly Gly His Arg
□
20 25 30
□

□
Gln Ile His Gln Val Arg Arg Gly Gln Cys Ser Tyr Thr Phe Val Val
□
35 40 45
□

□
Pro Glu Pro Asp Ile Cys Gln Leu Ala Pro Thr Ala Ala Pro Glu Ala
□
50 55 60
□

□
Leu Gly Gly Ser Asn Ser Leu Gln Arg Asp Leu Pro Ala Ser Arg Leu
□
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□

□
His Leu Thr Asp Trp Arg Ala Gln Arg Ala Gln Arg Ala Gln Arg Val
□
85 90 95
□

□
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□
100 105 110
□

□
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□
115 120 125
□

- 21 -

□
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□ 130 135 140
□

□
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□ 145 150 155 160
□

□
Val Glu Ala Gln Val Leu Asn Gln Thr Leu His Met Lys Thr Gln Met

□ 165 170 175
□

□
Leu Glu Asn Ser Leu Ser Thr Asn Lys Leu Glu Arg Gln Met Leu Met

□ 180 185 190
□

□
Gln Ser Arg Glu Leu Gln Arg Leu Gln Gly Arg Asn Arg Ala Leu Glu

□ 195 200 205
□

□
Thr Arg Leu Gln Ala Leu Glu Ala Gln His Gln Ala Gln Leu Asn Ser

□ 210 215 220
□

□
Leu Gln Glu Lys Arg Glu Gln Leu His Ser Leu Leu Asp His Gln Thr

□ 225 230 235 240
□

□
Gly Thr Leu Ala Asn Leu Lys His Asn Leu His Ala Leu Ser Ser Asn

□ 245 250 255
□

□
Ser Ser Ser Leu Gln Gln Gln Gln Gln Leu Thr Glu Phe Val Gln

□ 260 265 270
□

□
Arg Leu Val Arg Ile Val Ala Gln Asp Gln His Pro Val Ser Leu Lys

□ 275 280 285
□

-22-

□
Thr Pro Lys Pro Val Phe Gln Asp Cys Ala Glu Ile Lys Arg Ser Gly
□
290 295 300
□
□
Val Asn Thr Ser Gly Val Tyr Thr Ile Tyr Glu Thr Asn Met Thr Lys
□
305 310 315 320
□
□
Pro Leu Lys Val Phe Cys Asp Met Glu Thr Asp Gly Gly Trp Thr
□
325 330 335
□
□
Leu Ile Gln His Arg Glu Asp Gly Ser Val Asn Phe Gln Arg Thr Trp
□
340 345 350
□
□
Glu Glu Tyr Lys Glu Gly Phe Gly Asn Val Ala Arg Glu His Trp Leu
□
355 360 365
□
□
Gly Asn Glu Ala Val His Arg Leu Thr Ser Arg Thr Ala Tyr Leu Leu
□
370 375 380
□
□
Arg Val Glu Leu His Asp Trp Glu Gly Arg Gln Thr Ser Ile Gln Tyr
□
385 390 395 400
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Glu Asn Phe Gln Leu Gly Ser Glu Arg Gln Arg Tyr Ser Leu Ser Val
□
405 410 415
□
□
Asn Asp Ser Ser Ser Ala Gly Arg Lys Asn Ser Leu Ala Pro Gln
□
420 425 430
□
□
Gly Thr Lys Phe Ser Thr Lys Asp Met Asp Asn Asp Asn Cys Met Cys
□
435 440 445
□

-23-

□
Lys Cys Ala Gln Met Leu Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly

□ 450 455 460

□

□
Leu Ser Asn Leu Asn Gly Ile Tyr Tyr Ser Val His Gln His Leu His

□ 465 470 475 480

□

□
Lys Ile Asn Gly Ile Arg Trp His Tyr Phe Arg Gly Pro Ser Tyr Ser

□ 485 490 495

□

□
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□

□

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□ <211> 504

□ <212> PRT

□ <213> Human

□

□ <400> 6

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□ 1 5 10 15

□

□ Ala Thr Met Ser Val Ala Gln Gln Thr Arg Gln Glu Ala Asp Arg Gly

□ 20 25 30

□

□ Cys Glu Thr Leu Val Val Gln His Gly His Cys Ser Tyr Thr Phe Leu

□ 35 40 45

□

□ Leu Pro Lys Ser Glu Pro Cys Pro Pro Gly Pro Glu Val Ser Arg Asp

□ 50 55 60

□

-24-

Ser Asn Thr Leu Gln Arg Glu Ser Leu Ala Asn Pro Leu His Leu Gly
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□
Lys Leu Pro Thr Gln Gln Val Lys Gln Leu Glu Gln Ala Leu Gln Asn
□ 85 90 95
□
Asn Thr Gln Val Leu Lys Lys Leu Glu Arg Ala Ile Lys Thr Ile Leu
□ 100 105 110
□
Arg Ser Lys Leu Glu Gln Val Gln Gln Gln Met Ala Gln Asn Gln Thr
□ 115 120 125
□
Ala Pro Met Leu Glu Leu Gly Thr Ser Leu Leu Asn Gln Thr Thr Ala
□ 130 135 140
□
Gln Ile Arg Lys Leu Thr Asp Met Glu Ala Gln Leu Leu Asn Gln Thr
□ 145 150 155 160
□
Ser Arg Met Asp Ala Gln Met Pro Glu Thr Phe Leu Ser Thr Asn Lys
□ 165 170 175
□
Leu Glu Asn Gln Leu Leu Gln Arg Gln Lys Leu Gln Gln Leu Gln
□ 180 185 190
□
Gly Gln Asn Ser Ala Leu Glu Lys Arg Leu Gln Ala Leu Glu Thr Lys
□ 195 200 205
□
Gln Gln Glu Glu Leu Ala Ser Glu Leu Ser Lys Lys Ala Lys Leu Leu
□ 210 215 220
□
Asn Thr Leu Ser Arg Gln Ser Ala Ala Leu Thr Asn Glu Glu Arg Gly
□ 225 230 235 240
□

- 25 -

□
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□
245 250 255
□
□
Ser Leu Arg Gln Leu Leu Val Leu Arg His Leu Val Gln Glu Arg
□
260 265 270
□
□
Ala Asn Ala Ser Ala Pro Ala Phe Ile Met Ala Gly Glu Gln Val Phe
□
275 280 285
□
□
Gln Asp Cys Ala Glu Ile Gln Arg Ser Gly Ala Ser Ala Ser Gly Phe
□
290 295 300
□
□
Tyr Thr Ile Gln Val Ser Asn Ala Thr Lys Pro Arg Lys Val Phe Cys
□
305 310 315 320
□
□
Asp Leu Gln Ser Ser Gly Gly Arg Val Thr Leu Ile Gln Arg Arg Glu
□
325 330 335
□
□
Asn Gly Thr Val Asn Phe Gln Arg Asn Val Lys Asp Tyr Lys Gln Gly
□
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□
□
Phe Gly Asp Pro Ala Gly Glu His Val Glu Leu Gly Asn Glu Val Val
□
355 360 365
□
□
His Gln Leu Thr Arg Arg Ala Ala Tyr Ser Leu Arg Val Glu Leu Gln
□
370 375 380
□
□
Asp Val Glu Gly His Glu Ala Tyr Ala Gln Tyr Glu His Phe His Leu
□
385 390 395 400
□

- 26 -

□ Gly Ser Glu Asn Gln Leu Tyr Arg Leu Ser Val Val Gly Tyr Ser Gly
 □ 405 410 415
 □
 □ Ser Ala Gly Arg Gln Ser Ser Leu Val Leu Gln Asn Thr Ser Phe Ser
 □ 420 425 430
 □
 □ Thr Leu Asp Ser Asp Asn Asp His Cys Leu Cys Lys Cys Ala Gln Val
 □ 435 440 445
 □
 □ Met Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly Leu Ser Asn Leu Asn
 □ 450 455 460
 □
 □ Asp Val Tyr Tyr His Ala Pro Asp Asn Lys Tyr Lys Met Asp Gly Glu
 □ 465 470 475 480
 □
 □ Arg Val His Tyr Phe Lys Gly Pro Ser Tyr Ser Leu Arg Ala Ser Arg
 □ 485 490 495
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 □ Met Met Glu Arg Pro Leu Asp Glu
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- 27 -

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□
<400> 8
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□

29

8

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Claims:

1. A polynucleotide comprising a member selected from the group consisting of:

5 (a) a polynucleotide encoding the polypeptide as set forth in SEQ ID NO:2;
(b) a polynucleotide capable of hybridizing to and which is at least 70% identical to the polynucleotide of (a); and
(c) a polynucleotide fragment of the polynucleotide of (a) or (b).

10

2. The polynucleotide of claim 1 wherein the polynucleotide is DNA.

3. A vector containing one or more of the polynucleotides of claim 1 and 2.

15

4. A host cell containing the vector of claim 3.

5. A process for producing a polypeptide comprising: expressing from the host cell of claim 4 the polypeptide encoded by said DNA.

20

6. A polypeptide selected from the group consisting of

25

(a) a polypeptide having the deduced amino acid sequence of SEQ ID NO:2 and fragments, analogs and derivatives thereof, and
(b) a polypeptide comprising amino acid 1 to amino acid 493 of SEQ ID NO:2.

7. A pharmaceutical composition comprising the polypeptide of claim 6.

8. An antibody capable to bind to the polypeptide of claim 6.

30

9. Use of the polypeptide of claim 6 for the preparation of medicaments.

10. A diagnostic kit for the detection of the polypeptide of claim 6.

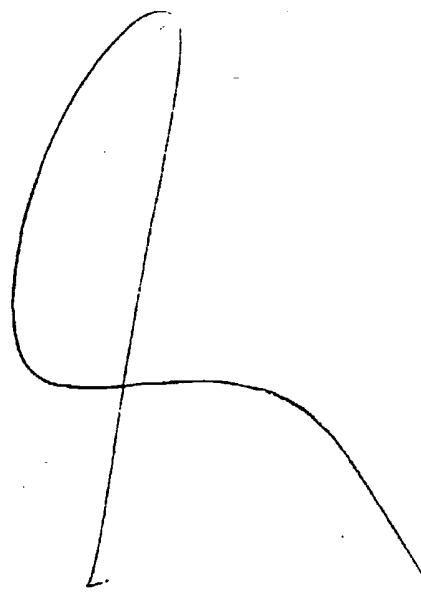
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02 Juli 1999

Angiopoietin-7 and uses thereof**Abstract**

The present invention provides an nucleic acid molecule encoding human Angiopoietin-7 (Ang-7) protein. In addition the invention provides methods for producing recombinant human Ang-7 protein. The invention also provides an antibody which specifically binds human Ang-7 protein. The invention further provides for therapeutic compositions as well as a method for modulating angiogenesis.



02 Juli 1999

Fig. 1: Sequence ID 1 (Ang-7)

GAAAATGAGG CTGCTGGGA CGGCTGAGG ATGAAACCCA AGCCCTGGAC CTGCCGACCG TGGCACTGAG 70
 GCAGCGGTG ACGCTACTGT GAGGGAAAGA AGGTTGTGAG CACCCCCCGA GGACCCCTGG CCAGCCCTGG 140
 CCCCAGCCTC TGGCGGAGCC CTCTGTGGAG GCAGAGCCAG TGGAGCCCG TGAGGCAGGG CTGCTGGCA 210
 GCCACCGGCC TGCAACTCAAG GAACCCCTCC AGAGGCCATG GACAGGCTCC CCCGCTGACG GCCAGGGTGA 280
 AGCATGTGAG GAGCCGCCCC GGAGCCAAGC AGGAGGGAAG AGGCTTCTAT AGTTTCTATT CACAAAGAAAT 350
 AACCAACATT TTGCAAAGAC CATGAGGCCA CTGTCGCTGA CATGCTGGTG GCTCGGACTG CTGGCTGCCA 420
 TGGGAGCTGT TGCAGGCCAG GAGGACGGTT TTGAGGGCAC TGAGGAGGGC TCGCCAAGAG AGTTTCTATT 490
 CCTAAACAGG TACAAGCGGG CGGGCGAGTC CCAGGACAAG TGCAACCTACA CCTTCATTGT GCCCCAGCAG 560
 CGGCTCACCG GTGCCATCTG CGTCAACTCC AAGGAGCTG AGGTGCTTCT GGAGAACCGA GTGCATAAGC 630
 AGGAGCTAGA GCTGCTCAAC AATGAGCTGC TCAACCCAGAA CGGCCAGATC GAGACGCTGC ACCAGCTGGT 700
 AACGGTGGAC GGCGGCATTG TGAGCGAGGT GAAGCTGCTG CGCAAGGAGA GCCGCAACAT GAACTCGGCG 770
 GTCACGCAGC TCTACATGCA GCTCTGCAC GAGATCATCC GCAAGCGGGG CAACCGCTTG GAGCTCTCCC 840
 AGCTGGAGAA CAGGATCTG AACCAGACAG CGGACATGCT GCAGCTGGCC AGCAAGTACA AGGACCTGGA 910
 GCACAGTAC CAGCACCTGG CCACACTGGC CCACACCCAA TCAGAGATCA TCGCCGAGCT TGAGGAGCCAC 980
 TGCCAGAGGG TGCCCTCGGC CAGGCCGTC CCCAGCCAC CCCCGCTCC CCCGCCCCGG GTCTACCAAC 1050
 CACCCACCTA CAACCGCATC ATCAACCCAGA TCTCTACCAA CGAGATCCAG AGTGACCAGA ACCTGAAGGT 1120
 GCTGCCACCC CCTCTGCCA CTATGCCAC TCTCACCCAGC CTCCCATCTT CCACCGACAA GCCGTCGGGC 1190
 CCATGGAGAG ACTGCCCTGCA GGCCCTGGAG GATGCCACG ACACCCAGCTC CTCCTACCTG GTGAAGCCGG 1260
 AGAACACCAA CGGCCCTCATG CAGGTGTGGT GCGACCCAGAG ACACCCACCC GGGGGCTGGA CGTCATCCA 1330
 GAGACGCCCTG GATGGCTCTG TTAACCTCTT CAGGAACCTGG GAGACGTACA AGCAAGGGTT TGGGAACATT 1400
 GACGGCGAAT ACTGGCTGGG CCTGGAGAAC ATTTACTGGC TGACGAACCA AGGCAACTAC AAACCTCTGG 1470
 TGACCATGGA GGACTGGTCC GGCGCAGAAG TCTTGTAGA ATACGCCAGT TTCCGCTGG AACCTGAGAG 1540
 CGAGTATTAT AAGCTGCGGC TGGGGCGCTA CCATGGCAAT GCGGGGTGACT CCTTACATG GCACAACGGC 1610
 AAGCAGTTCA CCACCCCTGGA CAGAGATCAT GATGTCTACA CAGGAAACTG TGCCCACTAC CAGAAGGGAG 1680
 GCTGGTGGTA TAACGCCCTGT GCGCCACTCCA ACCTCAACGG GGCTCTGGTAC CGCGGGGGCC ATTACCGGAG 1750
 CCGCTACCCAG GACGGAGCTCT ACTGGGCTGA GTTCCGAGGA GGCTCTTACT CACTCAAGAA AGTGGTGTG 1820
 ATGATCCGAC CGAACCCCAA CACCTTCCAC TAAGCCAGCT CCCCTCTCTG ACCTCTCGTG GCCATTGCCA 1890
 GGAGCCCACC CTGGTCACGC TGGCCACAGC ACRAAGAACAA ACTCCTCACC AGTTCATCCT GAGGCTGGGA 1960
 GGACCGGGAT GCTGGATTCT GTTTCCGAA GTCACTGCAG CGGATGATGG AACTGAATCG ATACGGTGT 2030
 TTCTGTCCCT CCTACTTTCC TTACACCCAG ACAGCCCCCTC ATGTCTCCAG GACAGGACAG GACTACAGAC 2100
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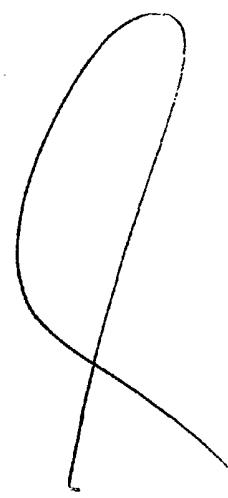


Fig. 2: Sequence ID 2 (Ang-7)

MRPLCVTCWW IGLLAAMGAV AGQEDGEFGT EEGSPREFIY LNRYKRAGES QDKCTYTFIV PQQVTGAIC 70
VNSKEPEVLL ENRVHKQELE LNNELLKQK RQIETLQQLV KVDGGIVSEV KLLRKESRNM NSRVTQLYMQ 140
LLHEIIRKRD NALELSQLEN RILNQTAADM LQASKYKOLE HKYQHLATIA HNQSEIIIAQL EEHCQRVPSA 210
RPVPQPPPAA PPRVYQPPPTY NRIINQISTN EIQSDQNLKV LPPPLPTMPT LTSLPSSTDK PSGPWRDCLQ 280
ALEDGHDTSS IYLVKPEINTN RLMQVWCQDR HDPGGWTVIQ RRLDGSVNFF RNWETYKQGF GNIDGEYWLG 350
LENIYWLTNQ GNYKLLVTME DWSGRKVFAE YASFRIEPES EYYKRLGRY HGNAGDSFTW HNGKQFTTLD 420
RDHDVYTGNc AHYQKGGWWY NACAHSMNLNG VVYRGGHYRS RYQDGVYWAE FRGGSYSLKK VVMMIRPNPN 490
TFH

493

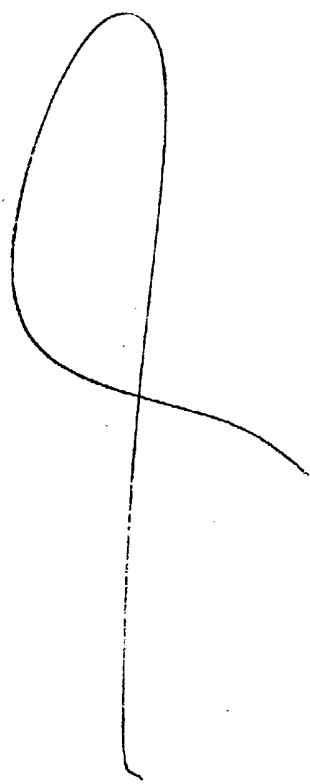
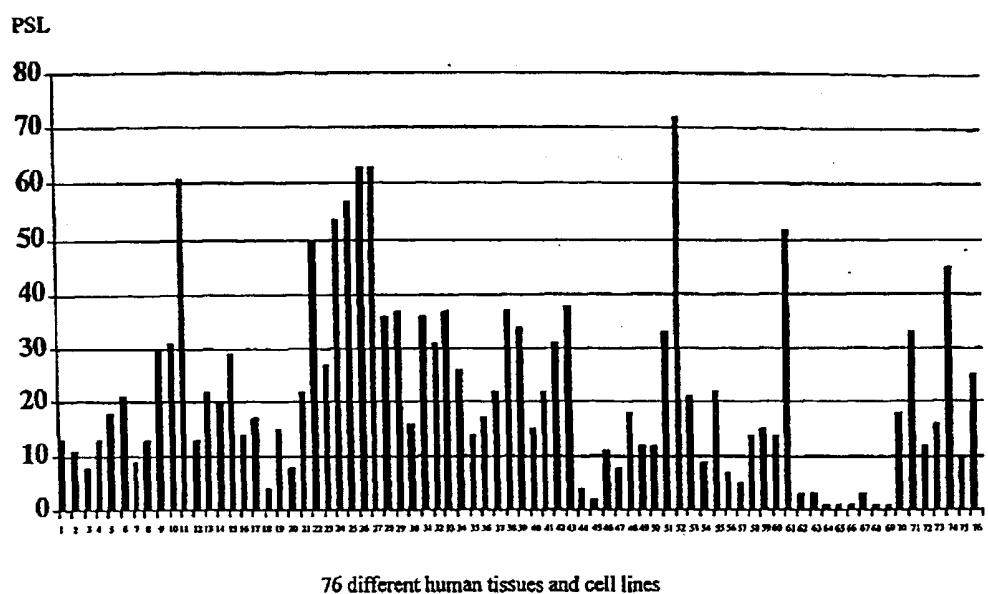


FIGURE 3

Decoration 'Decoration #1': Box residues that match the Consensus exactly

HANG-2.pro
HANG-3.pro
HANG-4.pro

Expression profile of Angiopoietin 7



- 1- whole brain
- 2- cerebral cortex
- 3- frontal lobe
- 4-parietal lobe
- 5-occipital lobe
- 6-temporal lobe
- 7-paracentral gyrus of cerebral complex
- 8-pons
- 9-cerebellum left
- 10-cerebellum right
- 11-corpus callusum
- 12-amygdala
- 13-caudate nucleus
- 14-hippocalamus
- 15-medulla oblongata

- 16-putamen
- 17-substantia nigra
- 18-accumbens nucleus
- 19-thalamus
- 20-pituitary gland
- 21-spinal cord
- 22-heart
- 23-aorta
- 24-atrium left
- 25-atrium right
- 26-ventricle left
- 27-ventricle right
- 28-interventricular septum
- 29-apex of the heart
- 30-esophagus
- 31-stomach
- 32-duodenum
- 33-jejunum
- 34-ileum
- 35-ilocecum
- 36-appendix
- 37-colon ascending
- 38-colon transverse
- 39-rectum
- 40-kidney
- 41-skeletal muscle
- 42-spleen
- 43-thymus
- 44-peripheral blood
- 45-lymph node
- 46-bone marrow

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- 47-trachea
- 48-lung
- 50-placenta
- 51-bladder
- 52-uterus
- 53-prostate
- 54-testis
- 55-ovary
- 56-liver
- 57-pancreas
- 58-adrenal gland
- 59-thyroid gland
- 60-salivary gland
- 61-mammary gland
- 62-Leukemia HL-60
- 63-HeLa S3
- 64-Leukemia K-562
- 65-Leukemia MOLT-4
- 66-Burkitt's lymphoma, Raji
- 67- Burkitt's lymphoma, Daudi
- 68-colorect. adenocarc. SW-480
- 69-Lung carcinoma A549
- 70-fetal brain
- 71-fetal heart
- 72-fetal kidney
- 73-fetal liver
- 74-fetal spleen
- 75-fetal thymus
- 76-fetal lung

Fig.4.

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Fig. 5

